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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/823,999	03/25/97	ROGERS	[illegible]

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EXAMINER	
[illegible]	

ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 11/23/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/4/98.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained ~~under the~~ provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-17 is/are pending in the application.

Of the above, claim(s) 7, 9, 13-17 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) ~~8~~ 1-6, 8, 10-12 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892 ☑ NOTICE TO COMPLY WITH SEQUENCE RULES

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1998-410-238/40050

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-12) in Paper No. 9 is acknowledged. The traversal is on the ground(s) that no additional effort is required to search Group II since the composition must be reached in order to search the methods of use. This is not found persuasive because of the reasons of record set forth in Paper No. 7.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 8, 10-12 and the species of antibodies to MAC-1 are under consideration as being drawn to the elected invention.

Accordingly, claims 7, 9 and 13-17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a nonelected invention

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825, however, this application fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Page 13, paragraph 3 of the instant specification discloses an amino acid sequence.

Applicant is required to fulfill these requirements by defining the SEQ ID NOS in both the specification and claims.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, including the specificity of claimed/elected compounds.

4. Formal drawings, filed 6/1/98, are acceptable.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 8, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo evidence of inhibiting leukocyte-integrin-mediated adhesion with Mac-1-specific antibodies accurately reflects the relative efficacy of the claimed methods relying upon any "compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion.

Although the claims are read in the context of the anti-Mac1 antibodies as the elected compound of the claimed invention; the following is noted as the claims read on "a compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion.

The instant claims encompass and are broadly drawn to "compounds" which encompass any compound, integrin, ligand, peptide or peptidomimetics capable of inhibiting or reducing leukocyte-integrin-mediated adhesion. However, the claims do not recite sufficient structural elements or specificity for the compounds encompassed by the claimed methods. The specification does not provide sufficient guidance and direction to identify and to enable any compound which might inhibit or reduce leukocyte-integrin-mediated adhesion. Additionally, all the claimed methods encompass in vivo administration of compounds, and as it has been well known to the skilled artisan that dosage parameters and administration protocols vary from molecule to molecule depending on clearance and reactivity of the molecule with internal factors. Therefore, in view of the breadth of the claims and the unpredictability in the art, and in view of the insufficient guidance and working examples in the specification, the quantity of experimentation required by one skilled in the art to practice the invention undue.

The following is noted with respect to inhibiting integrin-mediated inhibition.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of compounds which specifically inhibits or reduces leukocyte-integrin-mediated adhesion.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. Claims 1-6, 8 and 10-12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Coller et al. (U.S. Patent No. 5,770,198), as further evidenced by Simon et al. (Circulation, 1995). Coller et al. teaches the use of the 7E3 antibody to treat a number of thrombotic conditions (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7). Simon et al. provides evidence that the 7E3 antibody cross-reacts with Mac-1 (see entire document).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies.

11. Claims 1-6, 8 and 10 are rejected under 35 U.S.C. § 102(e) as being anticipated by Simon et al. (Circulation, 1995). Simon et al. teaches that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies.

12. Claims 1-6, 8, 10-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Ricevuti et al. (Artherosclerosis, 1991) AND/OR Albelda et al. (FASEB J., 1994) AND/OR Coller et al. (U.S. Patent No. 5,770,198) AND/OR Simon et al. (Circulation, 1995) in view of art known use of administering pharmaceutical reagents in various composition forms and at various intervention times and in further evidence of Neumann et al. (JACC, 1996).

Ricevuti et al. teaches inhibiting PMNs via anti-CD11b/CD18 antibodies to inhibit ischemia-reperfusion injury (see entire document, including the Abstract). This reference differs from the instant methods by not disclosing Mac-1-specific antibodies to inhibit restenosis and stenosis per se.

Albelda et al. teaches the use of adhesion molecule-specific including blockade of the CD11/CD18 complex has been show to inhibit neutrophil influx in almost every system to date including the heart and ischemia reperfusion (see entire document, including page 508, column 2, CD11/CD18).

Ricevuti et al. and Albelda et al. differ from the instant methods by not disclosing the use of Mac-1-specific antibodies to inhibit stenosis and restenosis per se, however such therapeutic methods would have readily discerned by the teaching indicated of inhibiting neutrophil influx and inflammation in ischemia-reperfusion injury.

Coller et al. teaches the use of the 7E3 antibody to treat a number of thrombotic conditions (see entire document, including Utility of Platlet-Specific Chimeric immunoglobulin in columns 5-7).

Simon et al. teaches that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Given the additional teachings of Coller et al. and Simon et al., the ordinary artisan would have motivation and expectation of success that the use of anti-Mac-1 specific antibodies would inhibit stenosis and restenosis associated with vascular intervention given that a property of the 7E3 antibody was to bind and inhibit via the Mac-1 specificity.

As further evidence that the Mac-1 specificity was an important target in treating complications associated with vascular intervention, Neumann et al. teaches the art known role of neutrophil and platelet activation, including the Mac-1 specificity.

The ordinary artisan would have applied different formulations and times of administration known and practiced at the time the invention was made to inhibit complications associated with vasculature intervention. The claimed formulations and times of administration were either taught by the references above or obvious to the ordinary artisan in treating different patients and different complications associated with different procedures.

One of ordinary skill in the art at the time the invention was made would have been motivated to select Mac-1 specific antibodies to inhibit restenosis and stenosis as a therapeutic regimen in treating complications associated with vascular interventions. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
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November 12, 1998